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ADDITIONAL MOLSIDOMINE IN REFRACTORY UNSTABLE ANGINA PECTORIS

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SUMMARY. In a prospective single-blind study we examined the effects of additional molsidomine in 20 patients (63 ± 10 years; 15 males, 5 females) with unstable resting angina (> 3 attacks/24 hours) refractory to triple therapy (nitrates, calcium antagonists, and beta blockers) combined with heparin or aspirin. All but one patient had coronary artery disease documented by coronarography (n = 17) or by recent myocardial infarction (n = 3). Two patients had angiographically documented severe coronary spasms. Patients entered the study if coronary bypass surgery or PTCA could not be performed within 3 days after angiography (n = 9) or was not feasible due to anatomical or technical reasons (n = 6), concomitant malignant disease (n = 2), or age greater than 75 years (n = 3). All patients received molsidomine orally 12 to 24 mg/day. In 15 of the 20 patients molsidomine was given i.v. initially, starting with 20 mg i.v., followed by infusion of 1 to 4 mg/hour. Heart rate and blood pressure did not change significantly, and eight patients had a slight decrease of systolic and diastolic blood pressure. Severe adverse effects did not occur, and moderate headaches were reported by five patients. In 13 patients, unstable angina could be stabilized, and they remained free of resting angina; five had a marked reduction of the frequency of anginal attacks. In two patients, molsidomine was without demonstrable beneficial effects. After a follow-up of 4 weeks, nine patients were free of symptoms after bypass surgery or PTCA, 10 continued to have angina NYHA class II or III, and one patient died due to acute myocardial infarction and cardiogenic shock 4 days after starting additional molsidomine. We conclude that molsidomine is well tolerated and has a marked beneficial effect in patients with refractory unstable angina. Molsidomine should therefore be considered for routine therapy of unstable angina, especially in those patients who are suspected of tolerance to nitrate therapy.

KEY WORDS. molsidomine, unstable angina, nitrates

The current management of patients with unstable angina pectoris aims at stabilization of symptoms by bed rest and medical treatment, including nitrates, calcium channel blockers, and beta blockers [1]. More recently, aspirin or heparin have become part of the standard therapy for the prevention of thrombotic events or platelet clots, which may promote additional anginal attacks or even myocardial infarction [2]. If medical therapy fails to prevent further ischemic episodes, bypass surgery or PTCA should be considered as therapeutic alternatives [3]. However, general guidelines as to the drugs of first choice and the efficacy of combination treatment in unstable angina pectoris are still lacking. We report favorable treatment results with additional molsidomine in patients with unstable angina refractory to triple therapy.

Patients

Twenty patients (15 males, 5 females; 63 ± 10 years) were included in the study. All had unstable angina with frequent painful episodes at rest and three or more attacks of rest angina during 24 hours before starting additional molsidomine treatment. At least once in each patient a typical ischemic pain episode was documented to correlate with ECG changes like ST segment depression (> 0.1 mV, n = 13), ST segment elevation (> 0.1 mV, n = 2), or T-wave inversion (n = 5). Diagnosis was coronary artery disease in 18 patients, based on clinical and angiographical findings in 17 patients and based on the history of proven recent Q-wave myocardial infarction in two patients. Two of the 20 patients had angiographically documented coronary spasms as the substrate for their ischemic pain. All patients were hospitalized, were restricted to bed rest, and continued to have rest angina despite the treatment combination of several drugs, as indicated in Table 1. All patients received nitrates and calcium channel blockers. Beta blockers were included definitively into the combination treatment in 15 of the 20 patients. Five received beta blockers only temporarily (range 24-72 hours), three of them had congestive heart failure and did not tolerate beta blockers, and in two patients (with coronary spasms) beta blockers had apparently no beneficial effects and therefore were omitted. All patients who entered the

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Table 1. Basic medical treatment of unstable angina in the 20 study patients before starting additional molsidomine. All patients received aspirin or heparin.

	n
Nitrates	20
—Nitroglycerine i.v 4 to 20 mg/hour	15
—ISDN 100 mg SR/day	5
Beta blockers	15 (20)
—Metoprolol 200 to 400 mg/day	12
—Atenolol 100 mg/day	3
Beta blockers temporarily (withdrawal after 24–72 hours)	
Ca antagonists	20
—Nifedipine 60 to 120 mg/day	7
—Diltiazem 180 mg/day	13

Table 2. Contraindications for PTCA or bypass surgery in 11 of the patients with unstable angina. Nine additional patients underwent PTCA or bypass surgery successfully.

	n
Anatomical reasons	4
Spasms	2
Malignant lymphoma	2
Age > 75 years/compromized general health status	3

study were not considered as candidates for PTCA or bypass surgery within the next 4 days. The reasons for the delay as well as the contraindications in the other patients are indicated in Table 2.

Assessment of Angina Pectoris

Fifteen of the 20 patients had a typical history of chronic stable angina, two had a recent onset angina (< 3 weeks), and three patients developed angina after their first myocardial infarction. Chest pain at rest was considered as angina if the patients reported it spontaneously, if it was documented by a written notice by the nurse, who was not aware of the aims of the study, and if the patient received additional analgesic treatment. Reports of angina were reviewed twice daily by an experienced physician. All patients were followed as to their symptoms during treatment until death or at least for 8 weeks. In those patients improving during therapy and having no further rest angina, a symptom-limited bicycle ergometry was performed at the end of the hospitalization, starting at 25 watts, with increments of 25 watts every 2 minutes.

Molsidomine Treatment

Molsidomine was given orally 12 to 24 mg/day. In 15 of the 20 patients, molsidomine was given i.v. initially, starting with 2 mg i.v., and then 1 to 2 mg/hour. The infusion was followed by oral medication. All other drugs were continued in unchanged dosages during the first 48 hours of the study.

Statistical Analysis

Changes in heart rate and blood pressure were evaluated using the student t test for paired data. The effects on the frequency of angina were tested according to Dixon and Mood [3].

Results

Effects of Additional Molsidomine on Angina Pectoris

Figure 1 indicates the effects of additional molsidomine on the symptoms of the patients. Eighteen patients were classified as responders, and two patients had no apparent favorable response and continued to have rest angina. One of these two patients died 4 days after starting molsidomine in cardiogenic shock, complicating an acute myocardial infarction. Nine of the 20 patients were finally treated by PTCA or bypass surgery and were free of angina 4 weeks later. Ten patients, classified as responders, continued to have NYHA classification grade II and III angina, but could be followed as outpatients.

Effects of Molsidomine on Blood Pressure and Heart Rate

Additional molsidomine did not change heart rate or blood pressure significantly. Only eight of the 20 patients exhibited a slight reduction of systolic and diastolic blood pressure, which was well tolerated (Figure 2).

Adverse Effects

No serious adverse effects of molsidomine were observed during the study. Aggravation of angina did not occur. Five patients reported moderate headaches after starting molsidomine.

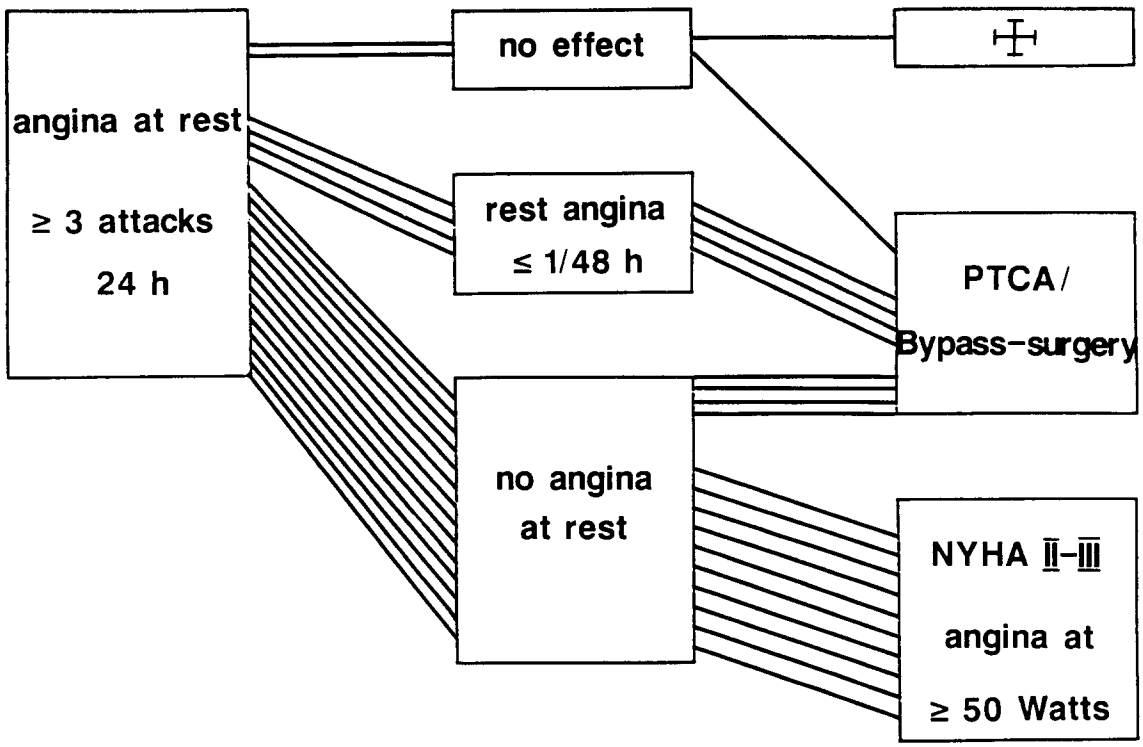

Fig. 1. Effects of additional molsidomine in refractory unstable angina pectoris as to the symptoms of the patients.

Discussion

Molsidomine had a marked anti-ischemic action in patients with coronary artery disease and symptoms on exertion, as established in numerous controlled studies [4-7]. For ethical reasons, we therefore conducted our study in a single-blind fashion without a placebo control group. The favorable treatment results, therefore, must be interpreted cautiously. However, the severity and frequency of angina pectoris attacks at rest in our patients before molsidomine make a spontaneous variability of angina unlikely as an alternative explanation for the marked symptomatic improvement. With respect to the complex medical therapy given to the patients as basic treatment, an additional placebo effect of molsidomine should be minimal.

Molsidomine had a marked beneficial effect on ischemic symptoms in our patients despite the complex pretreatment, including nitrates. As molsidomine acts in a similar way to nitrates on ischemic symptoms, our findings can be interpreted as a consequence of the better efficacy of this substance compared with nitrates or as a consequence of tolerance to nitrate therapy, at least in those patients receiving nitroglycerine infusion. In patients receiving nitroglycerine i.v., tolerance with fading nitrate effects has been shown to occur within 24 hours after starting treatment [9]. With respect to the limitations of continuous nitrate therapy and to the demonstrated effects of molsidomine in the present study, molsidomine can now be assessed in a controlled fashion against the currently used therapeutical alternatives without objections for ethical reasons.

Unstable angina is characterized by a high risk for acute myocardial infarction if left untreated [10-12]. Hospitalization of these patients and intensive treatment with beta blockers, calcium channel blockers, and nitrates combined with aspirin or heparin as preventive drugs have changed the prognosis substantially [13, 14]. Primary invasive therapy by PTCA or bypass surgery has not been shown to be superior thus

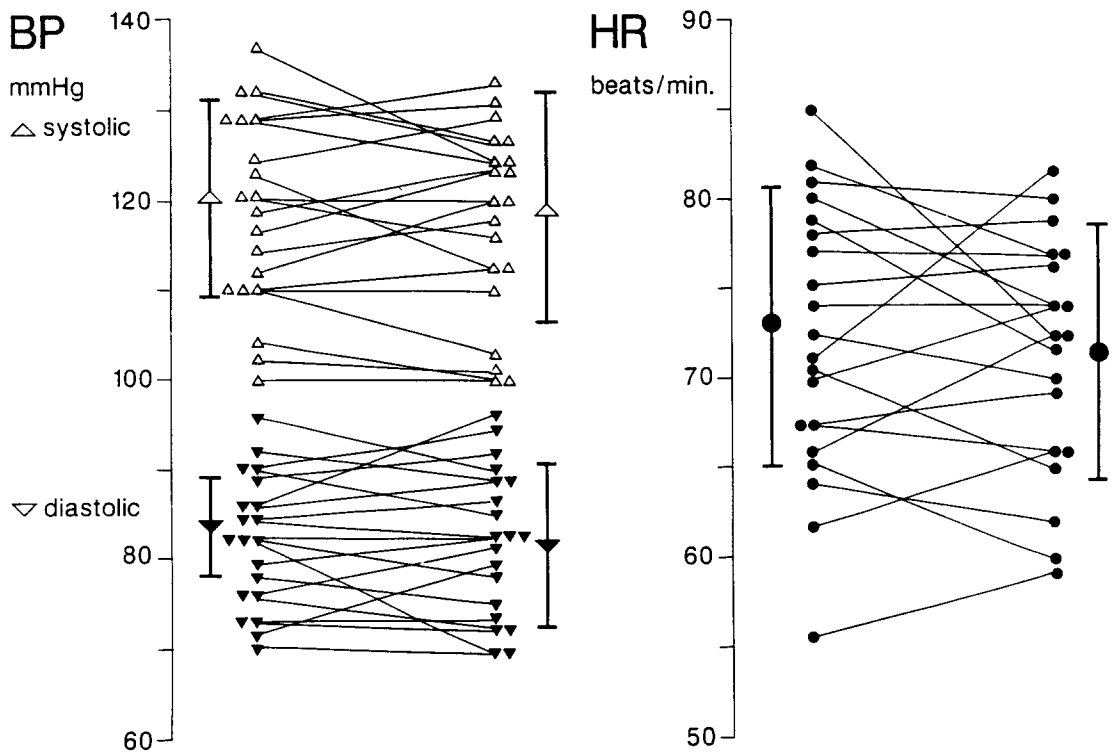

Fig. 2. Blood pressure and heart rate changes after additional molsidomine (4 hours) in refractory unstable angina pectoris ($\bar{x} \pm SD$).

far with regard to the patient's prognosis, when compared with medical treatment, if the stabilization of the symptoms by drugs alone can be achieved [14]. However, there is considerable disagreement as to the drug of first choice and to treatment combinations. Nitrates are commonly recommended as basic treatment, either as i.v. infusion or in formulations that can be given orally. Compared with calcium antagonists or beta blocker therapy, however, a 24-hour preventive effect against ischemic events cannot be achieved with nitrate therapy because of rapid development of tolerance in many, if not all, patients [9]. Therefore, a basic treatment of unstable angina with calcium antagonists combined with beta blockers in those patients without contraindications seems a reasonable alternative. Molsidomine can at least be added in patients refractory to this treatment, whereas nitrates should be given only intermittently to avoid tolerance.

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